



Modelling and prediction of the effect of operational parameters on the fate of contaminants of emerging concern in WWTPs



Marco Gabrielli^a, Riccardo Delli Compagni^a, Lucia Gusmaroli^{b,c}, Francesca Malpei^a, Fabio Polesel^d, Gianluigi Buttiglieri^{b,c}, Manuela Antonelli^a, Andrea Turolla^{a,*}

^a Politecnico di Milano, Department of Civil and Environmental Engineering (DICA), Piazza Leonardo da Vinci 32, 20133 Milano, Italy

^b Catalan Institute for Water Research (ICRA-CERCA), C. Emili Grahit 101, 17003 Girona, Spain

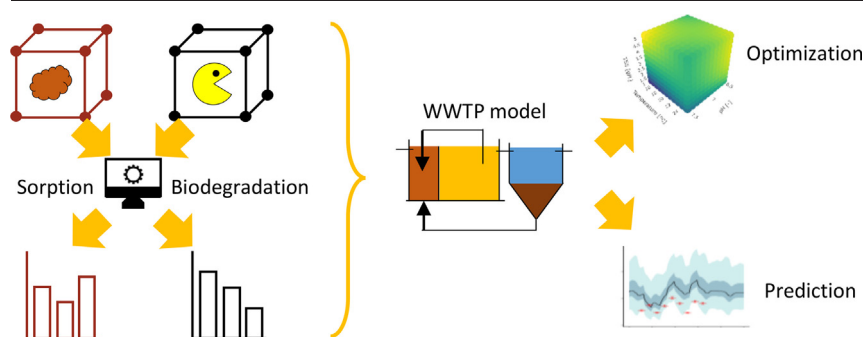
^c Universitat de Girona, Plaça de Sant Domènec, 3, 17004 Girona, Spain

^d DHI A/S, Artens Allé 5, 2970 Hørsholm, Denmark

HIGHLIGHTS

- The effect of WWTP parameters on sorption and biodegradation was assessed.
- Sorption and biodegradation are affected by WWTP parameters and their interactions.
- Most of the sorption variability can be explained by WWTP parameters.
- The dynamic daily patterns of pharmaceuticals were modelled in a full-scale WWTP.
- A site-specific approach to optimize WWTP operations was proposed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Paola Verlicchi

Keywords:

Emerging contaminants
Sorption
Biodegradation
Fate modelling
Activated sludge

ABSTRACT

Wastewater treatment plants (WWTPs) provide a barrier against the discharge of contaminants of emerging concern (CECs) into the environment. The removal of CECs is highly WWTP-specific and the underlying mechanisms are still poorly understood, hampering the optimization of biological treatment steps for their removal. To fill this knowledge gap, we assessed the influence of four operational parameters of activated sludge biological treatment, namely total suspended solids, temperature, pH and redox conditions, on the sorption and biodegradation of four CECs under controlled laboratory conditions. Design of Experiments was used to better address the factors influencing CECs removal and interactions among operational parameters. The derived statistical models showed results in concordance with previous studies and indicated how sorption and biodegradation of the investigated CECs depend on most tested parameters and few of their interactions. The predictions of the developed models have been compared with literature values, indicating how the tested parameters are responsible for most of the variability of sorption, while they could not reliably generalize biodegradation rates. The developed models were also implemented as an extension of a mechanistic biological treatment model, successfully describing the dynamic behaviour of a large-scale WWTP, which was observed during a three-day continuous monitoring campaign. Compared to a traditional modelling approach, the one including the developed models showed on average almost a three-fold uncertainty reduction, favouring its use to aid WWTP managers and regulators for improved assessment of CEC fate and removal. Finally, the models highlighted that, while higher temperatures and solids concentrations generically favoured CECs removal, removal efficiency vary significantly due to operational parameters and no globally optimum conditions for CECs removal exist. The use of these models opens the door to the combined dynamic management of both traditional contaminants and CECs in WWTPs.

* Corresponding author.

E-mail address: andrea.turolla@polimi.it (A. Turolla).

1. Introduction

Contaminants of emerging concern (CECs) are a group of substances linked with human activities, including pharmaceuticals and personal care products, endocrine disrupting agents, pesticides, natural and synthetic hormones (Daughton and Ternes, 1999). In untreated wastewater, CECs can be present at very low, but still relevant, concentrations (ng/L to µg/L), several of them exhibiting poor removal in wastewater treatment plants (WWTPs) and thus persisting in treated wastewater, potentially leading to an environmental and human health risk (Castaño-Trias et al., 2020).

For this reason environmental quality standards (EQS), or equivalent indicators, have been defined for specific CECs by, among others, the European Commission, Switzerland and Canada (Canada, 2021; European Commission, 2012; Swiss Federal Council, 2020). In addition, several other regulations apply to these substances due to their risk on human health in case of reuse of treated wastewater (Australia, 2008; California, 2019; European Commission, 2020). In fact, most WWTPs need to be retrofitted to meet such requirements, either installing tertiary treatments or upgrading/optimizing biological processes (Krzeminski et al., 2019). Activated carbon, high-pressure filtration (i.e., nano filtration and reverse osmosis) and ozonation are usually used for tertiary treatments, as, depending on configuration and operating conditions, have been shown to be highly effective in CECs removal (Rizzo et al., 2019). However, tertiary treatments can increase significantly operational costs (de Boer et al., 2022). For this reason, the upgrade and/or the optimal management of biological processes are attractive options to combine with or, even, substitute tertiary treatments to remove CECs with lower treatment costs and environmental impacts (Jones et al., 2007; Krzeminski et al., 2019).

Considering that the prominent phenomena involved in CECs removal by biological processes are sorption and biodegradation, solutions based on biological treatment optimization pose greater challenges for their management, as process performance is influenced by many factors, leading to highly WWTP-dependent removal (Tran et al., 2018). Among the factors affecting CECs fate in activated sludge (AS), the most common adopted biological treatment, most studies focused on the effect of temperature, pH, redox conditions or the solids retention time (SRT) on sorption and biodegradation either through laboratory experiments (e.g., Alvarino et al., 2014; Gulde et al., 2014; Meynet et al., 2020) or pilot/full-scale sampling campaigns (e.g., Hörsing et al., 2011; Petrie et al., 2014; Xue et al., 2010). However, these studies did not translate their experimental findings into generalized mathematical formulations describing the combined effect of the assessed factors on CECs fate. This is especially relevant as modelling tools are increasingly used by WWTP managers and by the scientific community for plant optimization and design (Hauduc et al., 2009) and several deterministic mathematical models have also been developed to describe CECs fate during AS treatment, either as ASM-like sub-models (Plósz et al., 2012; Vezzaro et al., 2014) or as stand-alone models (Struijs et al., 2016). The inadequate level of detail or the lack of mathematical formulations to describe the effect of the operational parameters on CECs fate has limited the application of these models. In fact, while a linear relationship between biodegradation rates and suspended solids concentration has been proposed in past models (e.g., Plósz et al., 2012; Delli Compagni et al., 2020a, 2020b), this assumption is not necessarily valid for a wide range of TSS concentrations (Hatoum et al., 2019). Furthermore, the effect of temperature on biodegradation rates (Ramin et al., 2016; Struijs et al., 2016) and the effect of pH on sorption (Nolte and Ragas, 2017) have been rarely included in models explicitly. The limited consideration given to the influence of operational parameters was also highlighted by Pomiès et al. (2013). Although this choice aims at reducing model complexity, which translates in fewer parameters and experimental data required, it limits the support that these tools can offer to WWTP managers to upgrade or optimize WWTPs towards maximum CEC removal. Despite the fact that general guidelines have been provided to achieve such goal (e.g., increasing the solid and hydraulic retention times - SRT/HRT, increase the suspended solids concentration or diversifying redox conditions, as proposed by

Krzeminski et al., 2019), little quantitative information is reported in literature, limiting their use in WWTPs upgrade/optimization.

In addition, to the best of the authors' knowledge, all laboratory experiments conducted so far focused on the effect of single parameters, neglecting possible interactions and, with the exception of Gusmaroli et al. (2020), varied singularly each of the operational parameters tested. Design of Experiments (DoE) represents a powerful statistical tool to assess and model the contribution of operational parameters and their interactions. Even though this approach is commonly used for industrial optimization (Weissman and Anderson, 2015) and has been used in few applications in the water and wastewater treatment field (Domínguez Henao et al., 2018; Ho et al., 2019), it has never been applied to model the effects of several operational conditions on CECs biodegradation and sorption. Following a DoE approach and contrarily to the previous studies, multiple parameters are varied simultaneously across two or more levels following a defined scheme in order to recover as much information as possible from a limited number of experiments and assess possible interactions between parameters (Montgomery, 2017).

To enhance the knowledge regarding CECs sorption and biodegradation, and to improve existing modelling approaches, this work presents (i) the use of a DoE approach to develop statistical models and estimate lab-scale sorption and biodegradation of eight CECs with different physical-chemical properties as a function of commonly measured operational parameters in activated sludge biological treatment (i.e., total suspended solids, temperature, pH and redox conditions), (ii) the validation of the developed DoE-based models using data retrieved from literature and (iii) the implementation of the developed DoE-based models in an ASM-based WWTP modelling framework to predict CECs measurements in a full-scale WWTP, and to estimate whether globally optimum conditions for CECs removal exist.

2. Materials and methods

2.1. Laboratory-scale data collection

Experimental data from sorption and biodegradation experiments was retrieved from Gusmaroli et al. (2020). Investigated CECs, namely clothianidin (CLT), diclofenac (DCF), estrone (E1), estradiol (E2), ethinylestradiol (EE2), erythromycin (ERY), methiocarb (MTC) and thiocloprid (TCP), were selected based on the priority list defined in the Commission Implementing Decision (EU) 2015/495. In brief, CEC sorption and biodegradation experiments were carried out varying pH, total suspended solids (TSS), temperature (Temp) and redox conditions (Redox) (hereafter generically referred to as operational parameters) following a full-factorial DoE design with two levels (High/Low) (Table 1) for a total of 16 combinations covering all the possible combinations of the tested operational parameters. Experiments were performed in continuously stirred reactors operated in batch mode for a duration of 6 h containing biomass inoculum from Celrà WWTP (Spain), after an initial spike of a mixture of all tested CECs at a nominal concentration of 2 µg/L, value comprised within the influent concentration range of most CECs (Tran et al., 2018). Samples were taken 30 s after spiking to allow mixing and then after 10 min, 1 h, 2 h and 6 h. Biodegradation experiments were conducted using freshly-sampled biomass in duplicated tests, while sorption experiments were performed in single replicates using autoclaved biomass. In both types of experiments the measurement of each sample was repeated twice. Analyses performed prior to the experiments indicated how the biomass presented negligible CECs concentrations before their execution.

2.2. Statistical analysis of laboratory-scale data

Data derived from both sorption and biodegradation experiments was cleaned from errors arising from insufficient initial mixing. In particular, when analysing the data of the sorption experiments, if the first measurement (30 s) resulted significantly lower than the following measurements, this value was discarded. When this issue was found in the processing of

Table 1

List of the experimental conditions derived by a full-factorial DoE. Oxidic conditions characterized by oxygen concentrations >2.5 mg/L, while anoxic conditions presented initial average NO₃⁻ concentrations of 74 mg N-NO₃⁻/L. Adapted from Gusmaroli et al. (2020).

Exp.	pH	TSS [g _{TSS} /L]	Temp [°C]	Redox
1	6.5	1	12	Anoxic
2	6.5	1	25	Anoxic
3	6.5	5	12	Anoxic
4	6.5	5	25	Anoxic
5	6.5	1	12	Oxic
6	6.5	1	25	Oxic
7	6.5	5	12	Oxic
8	6.5	5	25	Oxic
9	7.5	1	12	Anoxic
10	7.5	1	25	Anoxic
11	7.5	5	12	Anoxic
12	7.5	5	25	Anoxic
13	7.5	1	12	Oxic
14	7.5	1	25	Oxic
15	7.5	5	12	Oxic
16	7.5	5	25	Oxic

data from biodegradation experiments, the whole replicate was discarded (with the exception of E1). In any case, at most one replicate was removed for each biodegradation experiment, in order to preserve the integrity of the DoE design.

Solid-liquid partitioning coefficients K_d [L/g_{TSS}] were estimated as showed in Eq. (1) (Plósz et al., 2010b), where S_{CEC} indicates the CEC concentration at the first available sampling point (i) or at the last one (f), and C_{TSS} the concentration of TSS. In case experiments showed all measured concentrations within the 95 % confidence interval (CI) of $S_{CEC,i}$, K_d was considered as left-censored assuming a sorbed concentration equal to the range of $S_{CEC,i}$ uncertainty. The sorption equilibrium at the last sampling point assumed by Eq. (1) is supported by the fast kinetics reported by other studies (e.g., Banihashemi and Droste, 2014). While potentially some CECs could have sorbed to the sludge before the collection of the first sample, such waiting time was considered unavoidable as required to properly mix the spiked CECs in the reactors and provide representative concentrations.

$$K_d = \frac{S_{CEC,i} - S_{CEC,f}}{S_{CEC,f} \cdot C_{TSS}} \quad (1)$$

Pseudo-first order rate constants k_{bio} [L/(g_{TSS}·d)] were estimated through numerical fitting using Eqs. (2-a), (2-b), where X_{CEC} represents the sorbed CEC and k_{des} the desorption rate. To allow for a more reliable estimation of the biodegradation constant, during the fitting of each biodegradation experiment, the K_d value, which represent the ratio between sorption and desorption rates, was considered equal to the one obtained in the sorption experiment using the same combination of factors. The desorption rate (k_{des}) was assumed equal to 100 d⁻¹ (Plósz et al., 2010b) as this process is faster than the hydraulic retention times in WWTPs (Ternes and Joss, 2006; Banihashemi and Droste, 2014). In case of E1 and E2, the models of the two CECs were coupled considering the degraded E2 as completely transformed in E1 (Joss et al., 2004). The numerical fitting was conducted through the use of the Python library *LMFIT* v1.0.2 (Newville et al., 2014) by means of the Levenberg-Marquardt algorithm. To ensure that the global optimum fit was found, each experiment was fitted 100 times changing the initial values of the parameters following a Latin-hypercube sampling. The fit with the lowest root mean square error (RMSE) was deemed as optimal.

$$\frac{dS_{CEC}}{dt} = k_{des}X_{CEC} - k_{des}K_dS_{CEC}C_{TSS} - k_{bio}S_{CEC}C_{TSS} \quad (2-a)$$

$$\frac{dX_{CEC}}{dt} = -k_{des}X_{CEC} + k_{des}K_dS_{CEC}C_{TSS} \quad (2-b)$$

Kinetic constants corresponding to less than a 1 % degradation over 6 h were considered left-censored data assuming an upper bound equal to the k_{bio} that would result 1 % degradation (i.e., 0.04 L/(g_{TSS}·d) and 0.008 L/(g_{TSS}·d) for experiments with 1 and 5 g_{TSS}/L, respectively).

The final sorption and biodegradation datasets obtained are presented in Tables S1 and S2, respectively.

2.3. DoE-based models fitting

As both sorption and biodegradation experiments were conducted following a two-level full-factorial DoE design, multilinear statistical regression models were used estimate the coefficients of the operational conditions and their pairwise interactions (hereafter referred generically as predictors). Due to the presence of left-censored data, sorption and biodegradation DoE-based models were estimated by Maximum Likelihood Estimation (MLE) regressions (Cantoni et al., 2020; Helsel, 2011) considering the data as log-normally distributed using the R package *Survival* v3.2-7 (Therneau, 2020). The general formula of the developed models is shown in Eq. (3), where var represents the modelled variable (i.e., K_d or k_{bio}), $param$ the operational parameters values (Table 1), while $intercept$ and $coeff$ the fitted intercept and coefficients. The subscripts i and j indicate the operational parameters included in the model. In this model redox conditions were included exploiting a dummy binary variable to distinguish between the two states, where value of “1” indicates oxidic conditions.

$$\log(var) = intercept + \sum_i coeff_i \cdot param_i + \sum_{i,j} \sum_{i \neq j} coeff_{i,j} \cdot param_i \cdot param_j \quad (3)$$

Successively, predictors were removed from the initial DoE-based models following a backward AIC-based stepwise method, as implemented in *MASS* v7.3-53 (Venables and Ripley, 2002).

2.4. Validation of DoE-based models with literature data

The developed DoE-based models were tested against experimental values retrieved from literature lab-scale and full-scale studies considering conventional activated sludge (CAS) systems. Only studies in which all the relevant parameters used by the DoE-based models were specified and included within the tested factor levels (Table 1) were used for the comparison to avoid extrapolation. Experimental data derived from sludge originating from secondary settlers was not considered for validation of the sorption DoE-based models due to its weak statistical relationship with activated sludge possibly due to the strong influence of seldom-measured sludge characteristics, as proposed by Berthod et al. (2016). The full list of literature values is reported in Tables S3 and S4. Validation was carried out by comparing the experimental data with predicted values obtained from the DoE-based models using the values of operational parameters mentioned in each study.

2.5. Validation of DoE-based models with full-scale data

The proposed DoE-based models were validated against full-scale data derived from a different large-scale WWTP from the one in which the biomass was sampled for the lab-scale experiments. The full-scale WWTP sampled is located in northern Italy and has a capacity of 1,250,000 person equivalents. It treats predominantly domestic wastewater through a CAS biological treatment (pre-denitrification and oxidation/nitrification) without primary sedimentation. The average SRT during the sampling campaign was approximately 30 d.

Samples were collected for three consecutive dry-weather days in April 2019 as 8-hour time-proportional composites in refrigerated (4 °C) autosamplers (Hach Sigma SD900, Teledyne ISCO Avalanche, Teledyne ISCO 3700) at the inlet of the biological treatment (IN), between the anoxic and the aerated reactor (DN) in one of the treatment lines, and at the outlet of the secondary settler (OUT). Sampling was shifted between sampling sites considering the average HRT between each sampling point. The hourly sampled bottles were then mixed proportionally to the measured

Table 2

Gujer matrix of the processes included in the model to account for dissolved (S_{CEC}) and sorbed (X_{CEC}) CECs and their conjugate glucuronides ($S_{\text{CEC, conj gluc}}$).

	S_{CEC}	X_{CEC}	$S_{\text{CEC, conj gluc}}$	Process rate [1/d]
Deconjugation	$+f_{\text{dec}}$		-1	$k_{\text{dec}} \cdot C_{\text{TSS}} \cdot S_{\text{CEC, conj gluc}}$
Sorption	-1	$+1$		$K_d \cdot k_{\text{des}} \cdot C_{\text{TSS}} \cdot S_{\text{CEC}}$
Desorption	$+1$	-1		$k_{\text{des}} \cdot X_{\text{CEC}}$
Biodegradation	-1			$k_{\text{bio}} \cdot C_{\text{TSS}} \cdot S_{\text{CEC}}$

influent flowrate to obtain representative flow-proportional 250 mL composite samples. Special attention was given on limiting biodegradation within the sampling buckets. Preparatory tests were employed to confirm the absence of bias related to the sample procedure implemented.

Aliquots of each flow-proportional composite sample were filtered with 0.45 μm PVDF membranes (Durapore®, Merck Millipore), eventually after a pre-filtration with GF/A (Whatman®, Sigma-Aldrich) membranes, and frozen until analysis. The dissolved CECs concentration was measured by means of online SPE-UHPLC-MS/MS according to the method described in Gusmaroli et al. (2018). Filtered samples were analysed for soluble chemical oxygen demand (sCOD), ammonium (NH_4^+), and nitrate (NO_3^-) using the appropriate Hach Lange kits (LCK1414/LCK614, LCK304/LCK303 and LCK339, respectively). An unfiltered aliquot of each flow-proportional composite sample was used to determine TSS, total chemical oxygen demand (COD) and total nitrogen (TN). TSS were measured filtering samples on 0.45 μm membranes, while COD and TN were measured using the LCK1414/LCK614 and LCK238 Hach Lange kits, respectively. In addition, the concentrations of conventional pollutants (COD, NH_4^+ , NO_3^-), the pH at the inlet and outlet of the WWTP, TSS and the dissolved oxygen in the aerobic reactors were provided by the WWTP operators, together with online sensors data regarding the influent flowrate (1-h frequency) and the biological reactors temperature (5-minute frequency).

The model of the biological section of the full-scale WWTP was derived from Delli Compagni et al. (2020b). The model was implemented in WEST 2020 (DHI A/S, Denmark) using an ASM2d-based process model and conceptualizes the WWTP as a single line, with volumes and surface areas corresponding to the sum of all process lines (anoxic tank: volume = 50,000 m^3 ; aerated tank: volume = 152,000 m^3 ; settler: area: 175,000 m^2 , height: 5.5 m). The concentration of the conventional pollutants (COD, NH_4^+ , NO_3^- , TSS) was used to calibrate the WWTP model through the regulation of few selected influent, process and biokinetic parameters, following good modelling practice guidelines (Rieger et al., 2013). Sludge temperature and pH were set equal to the measured values.

The ASM2d model was extended to model the fate of CECs implementing the processes included in Table 2, similarly to Delli Compagni et al. (2020b). Simulations were carried out only for E1, E2, DCF and ERY, the only CECs with concentrations above the limit of quantification (LOQ) at the WWTP inlet. Similarly to batch experiments, all the degraded E2 was considered as transformed into E1. Since the lab-scale experiments were carried out using only the parent CECs, the deconjugation rate values (k_{dec}) were retrieved from literature, while the fraction of conjugates that transforms back to the parent compound (f_{dec}) was assumed equal to 1 (Joss et al., 2004; Plósz et al., 2012; Delli Compagni et al., 2020a, 2020b). On the other hand, K_d and k_{bio} were estimated dynamically depending on the simulated condition by implementing the DoE-based models equations in the WWTP model, assuming, as done during the fitting of the lab-scale data, k_{des} equal to 100 d^{-1} (Plósz et al., 2010b). As the measured influent concentrations refer only to the dissolved CECs fraction, primary sludge K_d values and parent/metabolites ratios were derived from literature either directly or from the reported CECs and metabolites concentrations (Berthod et al., 2016; Delli Compagni et al., 2020b; Joss et al., 2004; Verlicchi et al., 2012). These values were used to estimate the concentration of conjugate glucuronides and sorbed CECs at the inlet of the

biological treatment based on the measurements of the dissolved influent CECs concentrations. Such measured and estimated concentrations were used as input to the model assuming a step-like behaviour synchronized with the time of composite samples collection.

2.5.1. DoE-based and literature-based uncertainty analyses

An uncertainty analysis was carried out using a forward Monte Carlo approach (1000 simulations), sampling randomly the sorption and biodegradation DoE models coefficients according to the multivariate gaussian covariance structure provided by the MLE regressions (hereafter referred to as DoE-based uncertainty analysis). Furthermore, the uncertainty of the inlet dissolved CEC concentration was included in the analysis and considered equal to what specified in the measurement method (Gusmaroli et al., 2018). Due to the scarcity of experimental literature data, the uncertainty of few parameters regarding both CECs' fate within the WWTP and the partitioning of the influent CECs was determined through an expert-based evaluation of the data sources by assigning a percentage of variation (PV). A PV equal to 100 % was assigned to the proportion of metabolites present at the inlet of the WWTP, while a PV equal to 50 % was attributed to the metabolites degradation rates and the fraction of sorbed CECs at WWTP inlet. The PVs were then used to estimate the minimum and maximum value for each parameter which were used as extremes of uniform probability distributions.

To compare the benefits of the proposed model DoE-based models, a secondary uncertainty analysis (hereafter referred to as literature-based uncertainty analysis) was carried out using the same model but assigning static sorption (K_d) and biodegradation (k_{bio}) constants based on literature values (Tables S5–S6). Depending on the availability of the data, the distribution of parameters was assumed triangular or uniform, as in Delli Compagni et al. (2020a). Uniform distributions were used in case that less than three literature values were found. In case of ERY, for which only a single value was found, the extremes were set assuming a PV equal to 50 %, while the extremes were set equal to such values when two values were retrieved. Otherwise, triangular distributions were assumed setting minimum and maximum values as extremes and the median as the mode. Except the values of K_d and k_{bio} , all the other details in the literature-based uncertainty analysis were considered equal to the ones used in the DoE-based one to highlight only the effect of the affected parameters.

The results of both uncertainty analyses were quantitatively compared to the obtained data by estimating absolute difference between the measured flow proportional composite samples and the simulated ones. Simulated composites have been estimate using the hourly flow data measured at the sampled WWTP and the simulated concentrations of each uncertainty simulation run. In order not to take into account only the accuracy of the simulated samples, but also their precision, both the average and the standard deviation of the differences were estimated.

2.6. Exploration of the effect operational parameters effect on full-scale CECs removal

Steady state simulations were carried out for each CEC varying pH, Temp and TSS within both anoxic and aerobic reactors covering uniformly the parameter space explored by the analysed laboratory experiments and explore the effect of the change of operational parameters on the fate of CECs in full-scale WWTPs. To assess the results reliability, a reduced Monte Carlo uncertainty analysis (10 simulations) was carried out on 100 randomly selected operational parameters combinations. In addition, another set of simulations was carried out following a hypothetical scenario in which, even though maintaining the same overall WWTP volume, the anoxic HRT of the modelled WWTP was halved. For each simulation, the overall removal rate, estimated using influent and effluent CECs loads, and the normalized waste sludge CECs concentrations were estimated considering both soluble and sorbed CECs fractions.

3. Results and discussion

3.1. Operational conditions affecting sorption and biodegradation

The numerical fitting of the dissolved CECs concentration profiles provided satisfactory results (average root mean square error, RMSE = 78.8 ng/L, Table S7, Figs. S1–S7) allowing the development of the DoE-based models. As the experimental plan of Gusmaroli et al. (2020) comprised of two levels for each operating condition, the DoE-based models permitted to obtain a linear estimate of the effect of the varied operational parameters and their pairwise interactions within the tested ranges. Fig. 1 and Tables S8 and S9 show the values of the parameters of the DoE-based models obtained for each investigated CEC (i.e., $coeff_i$ in Eq. (3)). Positive values indicate that an increase in the numerical value of the predictors is linked with an increase in K_d or k_{bio} , while negative values indicate the opposite. The developed models indicate how most predictors are relevant for the estimation of the sorption and biodegradation behaviour of the investigated CECs. The variability of the predictors values among the different CECs can be attributed to their different chemical structures and physical-chemical properties, which affected their interactions with the activated sludge and their (co)-metabolism (Berthod et al., 2016; Kennes-Veiga et al., 2022; Nolte et al., 2020).

3.1.1. Redox

The variation of redox conditions significantly influenced the CECs partitioning coefficient, in line with what observed by lab-scale experiments conducted by de Wilt et al. (2018) and full-scale data collected by Xue et al. (2010). Furthermore, in accordance with Pomiès et al. (2013), the presence of aerobic conditions showed generically a positive effect on biodegradation rates. A notable exception is E2 which exhibited faster biodegradation under anoxic conditions, confirming what reported by Joss et al. (2004) and Xue et al. (2010). Such difference arises from the presence of redox-dependent degradation microorganisms and pathways which are related to the chemical structure of each CEC (Chiang et al., 2020). For example, depending on the redox conditions, E2 can be degraded to E1 in aerobic and anoxic conditions, while the opposite occurs in anaerobic

conditions as the result of different enzymatic reactions (Joss et al., 2004; Kennes-Veiga et al., 2022).

3.1.2. TSS

Mass-transfer limitations caused by higher solids concentrations are likely responsible for the negative effect of TSS on sorption. In fact, higher TSS concentration could have led to larger flocs and reduced local mixing conditions, limiting CECs to reach sorption sites (Hatoum et al., 2019). This result suggests that the assumption of linear sorption linked with the use of K_d might not be appropriate and that non-linear sorption isotherms (e.g., Freundlich) (Clara et al., 2004; Hörsing et al., 2011; Polesel et al., 2015) might be preferred to model CEC sorption. Regarding biodegradation, even though pseudo first-order rate constants are commonly used to compare WWTPs with different TSS concentrations (Pomiès et al., 2013), the presence of biodegradation coefficients for TSS different than zero suggests that this approach might not be completely accurate. Such result is in accordance with the sub-linear increase in first-order k_{bio} values at increasing TSS concentrations observed for few CECs by Hatoum et al. (2019). This sub-linearity is likely also caused by mass-transfer limitations determined by the higher TSS concentrations which would have limited the CECs availability to microbes, similarly to what hypothesized for sorption. On the other hand, even though observed also in Collado et al. (2012), no obvious explanation for the positive effect of an increase of TSS on k_{bio} was found.

3.1.3. pH

Sorption and biodegradation have often been related in the literature with the compound uncharged fraction (Tadkaew et al., 2010; Urase and Kikuta, 2005), but, with the exception of TCP ($pK_b = 7$) and ERY ($pK_a = 8.6$), the range of pH tested is >2 pH-units distant from the pK_a of the other CECs. For this reason, the pH variation tested is expected to have a limited effect on the speciation of such CECs (Clara et al., 2004; Tadkaew et al., 2010). As a consequence, K_d variations are likely due to changes in the structure of the activated sludge (Hörsing et al., 2011; Sürücü and Çetin, 1990), which could have affected the availability of sorption sites. Also the various electrostatic interactions which arise between the cationic-neutral CECs and sorbents can be influenced by a variation of pH

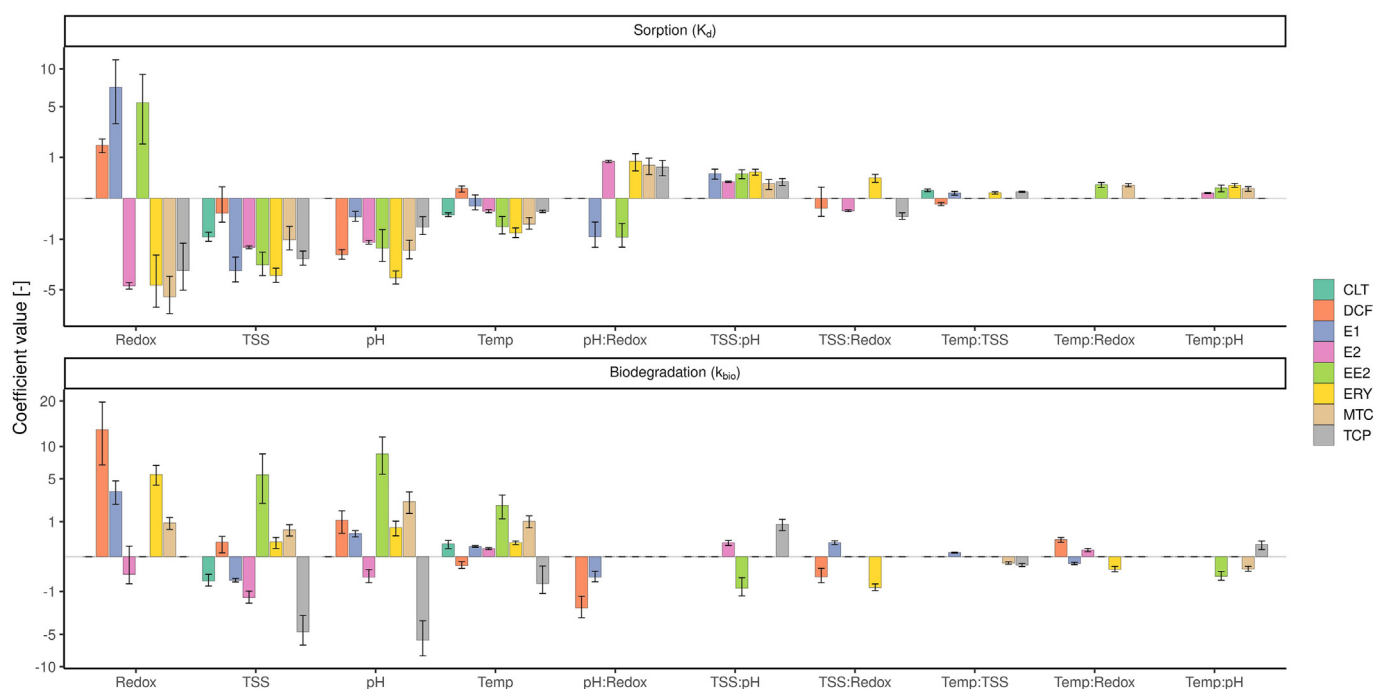


Fig. 1. Estimated values and standard deviations of the coefficients of the DoE-based models. A squared root transformation was applied to the vertical axis to improve readability.

(Gulde et al., 2014). The increase of pH resulted in both positive and negative effects on biodegradation rates. A possible reason could be that different pH conditions altered the activity of microorganisms thus affecting the biodegradation rate (Gulde et al., 2014; Tran et al., 2013; Zhang et al., 2005). Surprisingly, an increase in the undissociated fraction of TCP at high pH was found to be related with slower biodegradation. However, as noted by Gulde et al. (2014), the biotransformation mechanisms for cationic-neutral CECs are not simply related to the fraction of undissociated CECs, but are impacted by several pH-dependent processes.

3.1.4. Temperature

Except for DCF, CECs sorption was negatively affected by the increased temperature. Such result aligns with literature studies (Xu et al., 2008; Zhou et al., 2013), showing that sorption is favoured at lower temperatures, being an exothermic process. The different behaviour of DCF is likely due to confounding effects influenced by temperature, e.g., solubility, viscosity and diffusion rates, whose interaction can alter the ability of molecules to move across the particles boundary layer, affecting thus the sorption equilibrium. In fact, endothermic sorption has been recorded in soil organic fraction (Xu et al., 2021) and carbonaceous materials (Zhang et al., 2020). Furthermore, this result could be also influenced by the possible modification of the biomass structure during the experiments, as no previous biomass acclimatization was performed. On the other hand, the positive effect of an increased temperature on biodegradation seems to be generically in accordance with experimental studies (e.g., Li et al., 2005) and the use of an Arrhenius-type model due to the increase in bacterial activity at higher temperatures (Ramin et al., 2018; Kennes-Veiga et al., 2022). A recent study (Meynet et al., 2020) has, however, shown how the classic formulation of the Arrhenius model is not valid for all CECs, as, in some cases, k_{bio} was shown to decrease above 20–30 °C due to changes in the microbiological communities present and, in particular, to the variations of the abundance and activity of few selected taxa. Such phenomena could explain the negative temperature coefficients for DCF and TCP. Alternative formulations (e.g., Ratkowsky-based), describing reduced microbial activity at high temperatures, may be of relevance (Guo and Vanrolleghem, 2014).

3.1.5. Interactions

It is interesting to note how interactions between the operational parameters have also an effect on the biodegradation and, particularly, on the sorption of CECs. Notably, the interaction between pH and other operational parameters seems to affect sorption coherently, suggesting similar phenomena influencing the removal of most of the CECs investigated, independently of their molecular structure. Such phenomena are likely to depend on the variations in the activated sludge properties, as for example changes in the flocs surface charge. To the best of the authors' knowledge, this is the first time the relevance of such interactions has been reported.

It has to be noted that as the experimental design performed by Gusmaroli et al. (2020) was limited to two levels per operational parameter, the current work is limited to describe linear responses and cannot detect non-linearities responses due to the parameters variation. While designing more complex DoE involving more than two levels is possible, the number of experiments and thus costs required would increase exponentially, possibly leading to the reduction of the number of experimental factors considered. Nonetheless, initial DoE schemes could be further expanded in future investigations by additional experiments, allowing to refine the description of the effect of the parameter of interest.

3.2. Performance of DoE-based models to predict literature data

The developed DoE-based models were used to predict sorption coefficients and biodegradation rate constants retrieved from literature. Most of the literature K_d values were predicted with good accuracy, as shown in Fig. 2a, implying that the operational parameters used in the developed

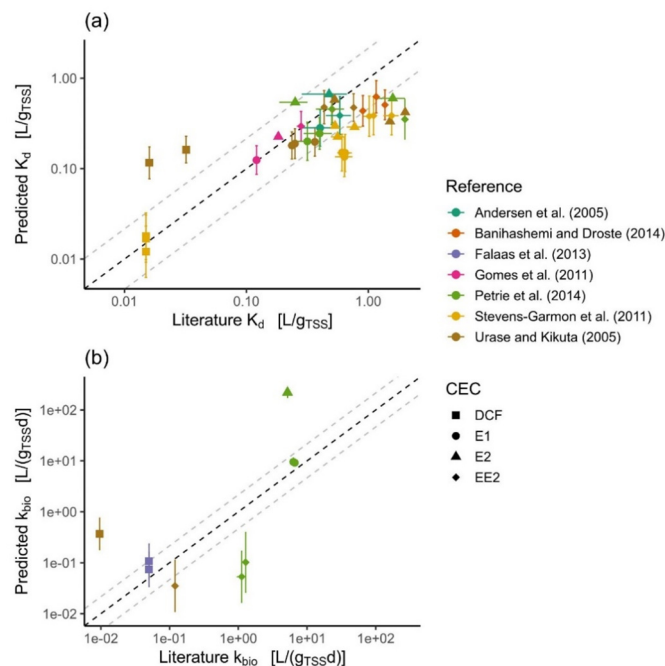


Fig. 2. Sorption (a) and biodegradation (b) constants derived from literature and estimated using the developed DoE-based models. The black dashed line marks the 1:1 correspondence, while the grey lines correspond to the 1:3 and 3:1 ratios.

DoE-based models are sufficient to predict most of the sorption variability regardless of the specific WWTP. Other than to differences in sampling and analytical protocols, the residual variability is likely caused by other sludge parameters not taken into account by the proposed models as, for example, the fraction of organic carbon, the granulometry and the content of specific organic fractions (Barret et al., 2010; Sathiamoorthy and Ramsburg, 2013).

On the contrary, literature k_{bio} values were found to be predicted less accurately (Fig. 2b), even though presenting a generic concordance with the literature data (Pearson correlation coefficient = 0.51). Indeed, CECs biodegradation rates in WWTPs are notoriously difficult to predict, even if coming from a single WWTP (Blair et al., 2013). Less accurate predictions result could be partly explained by the previously mentioned absence of acclimation, sampling and analytical protocols, and other experimental factors (e.g., dosage of readily available substrates). Nonetheless, the lower accuracy can also be explained by the fact that the biodegradation rates are highly affected by the microbiome (Achermann et al., 2020) and the taxonomical richness (Johnson et al., 2015) present in WWTPs. In fact, the microbiome is highly dependent on both influent chemical characteristics, but also other parameters, including SRT (Krzeminski et al., 2019) and geographical area (Wang et al., 2012). For this reason, the extrapolation of biodegradation rates to other WWTPs, even if considering the different operational parameters, might not always be acceptable. Plausibly, ensuring the biomass acclimation and the use of more fine-grained data, including details regarding the biomass activity, the nitrification potential or the microbiome composition, would lift the current limitations and provide better predictive performances. However, the complexity and the time required to perform such analyses are likely to limit the adoption of models requiring their estimation. In fact, the operational parameters used in this study were chosen to be easily measured daily or in real time potentially enabling these models to be used as a management tool to track CECs removal performances and trigger ad-hoc interventions (e.g., powdered activated carbon dosage). Another alternative to better generalize the predictions regarding CECs biodegradation in future studies could be the exploitation of black box models (e.g., artificial neural networks). However, such tools would not allow to obtain an explicit understanding of the effects of the

operational conditions and interactions, contrarily to the approach chosen in this work.

Still, as CECs biodegradation was shown to be affected by site-specific characteristics, other than the operational parameters tested, we speculate that the comparison of DoE-based models developed based on the data originating from different WWTPs would allow to distinguish between the effect of general physical or biochemical processes and site-specific effects, possibly providing fruitful insights in the understanding of this process. For example, similar coefficients for the same operational parameter across different WWTPs could highlight which are not altered by the different activated sludge composition or microbial communities. On the other hand, highly fluctuating coefficients would suggest a strong dependence on site-specific conditions.

3.3. Comparison of DoE-based and literature-based models to predict CECs fate in a full-scale WWTP

Even though the developed DoE-based models were shown to provide an accurate and generalized prediction only for sorption constants and not biodegradation, it was still decided to test their performance for the simulation of full-scale WWTPs. Such choice was supported by the fact that, as long as several parameters (including K_d and k_{bio}) present values in appropriate regions, the accuracy of full-scale WWTPs simulation show limited sensitivity to the precise parameters values used (Baalbaki et al., 2017b).

Even though not the focus of this study, a good model calibration with respect to TSS and conventional pollutants is a required step prior to CEC modelling (Baalbaki et al., 2017a). The calibrated concentrations of TSS and conventional pollutants in the full-scale WWTP were in good

agreement with measurements (Fig. S8). Among the measured conventional pollutants, only the simulated concentration of NH_4^+ at sampling point DN showed a deviation from the measurements. Such result is likely due to the possible contamination of the DN samples with water from the aerated reactor, as this sample was collected in the aerated reactor in correspondence with the submerged opening that connects the anoxic and aerated reactors. Special care was paid to the calibration of TSS which directly influence CEC fate in both sorption and biodegradation equations.

The predicted CEC concentrations and related uncertainty derived by the DoE-based and the literature-based models are shown respectively in Figs. 3 and 4. The DoE-based models generally resulted in higher concentrations than measured at sampling point DN, while CECs at the outlet of the secondary settler (OUT) remained at concentrations either in line or slightly below measured values, indicating an underestimation of the removal in anoxic conditions and an overestimation in aerobic ones. In contrast, the use of literature-based models led to a better prediction of E1 at sampling point DN, but underestimated and overestimated the removal of, respectively, DCF and ERY in the anoxic reactor and overpredicted the removal of all CECs in aerobic conditions. Notably, literature-based models showed uncertainty bands whose width is between 1.04 and 2.85 times the DoE-based one, except for ERY at sampling location DN. Interestingly, both models highlighted the presence of daily patterns in the CECs concentrations, which are supported by measurements, likely due to different CECs consumption, metabolization and excretion rates, as reported for other WWTPs (Plósz et al., 2010a), resulting in variations in the inlet concentrations throughout the day. While such fluctuations are evident in the inlet CECs concentrations (Fig. S9) of the WWTP they are also evident within the plant, especially in case of ERY and E2. Noteworthy, these patterns are smoothed in the effluent water (OUT), limiting possible acute

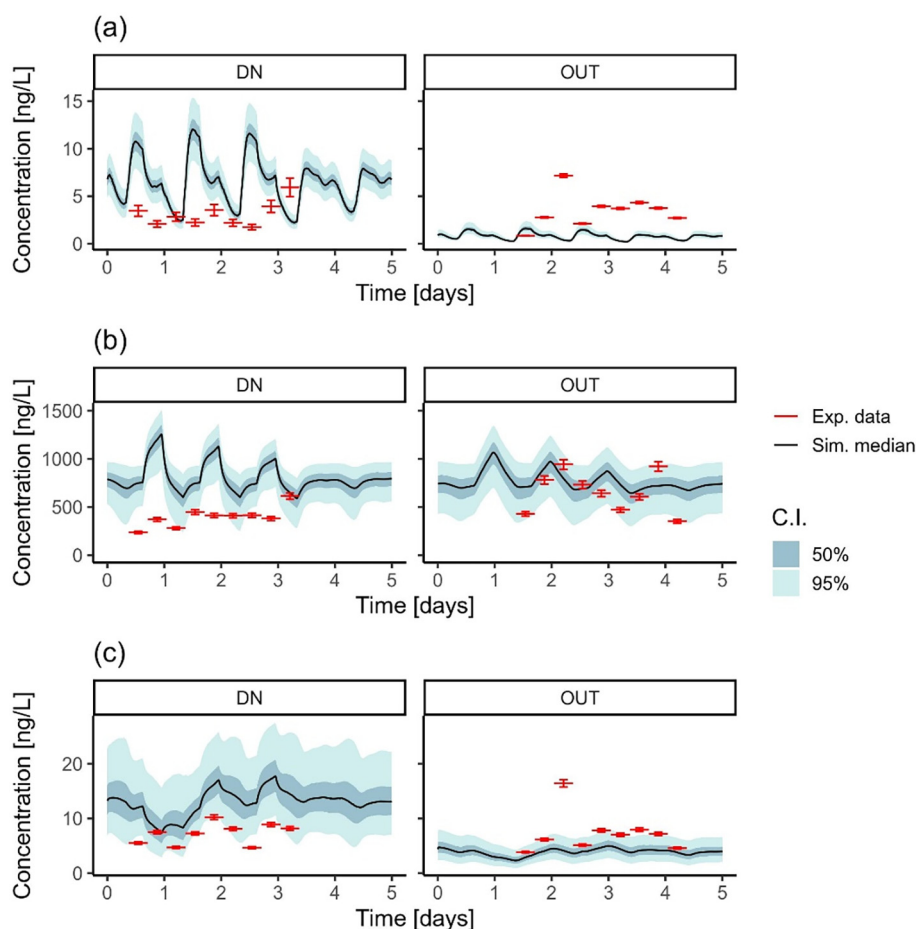


Fig. 3. Measurements and predictions of the DoE-based models of E1 (a), DCF (b) and ERY (c) concentrations between the anoxic and aerated reactors (DN) and at the outlet of the secondary settler (OUT). E2 is not shown as present at concentrations below LOQ at both DN and OUT.

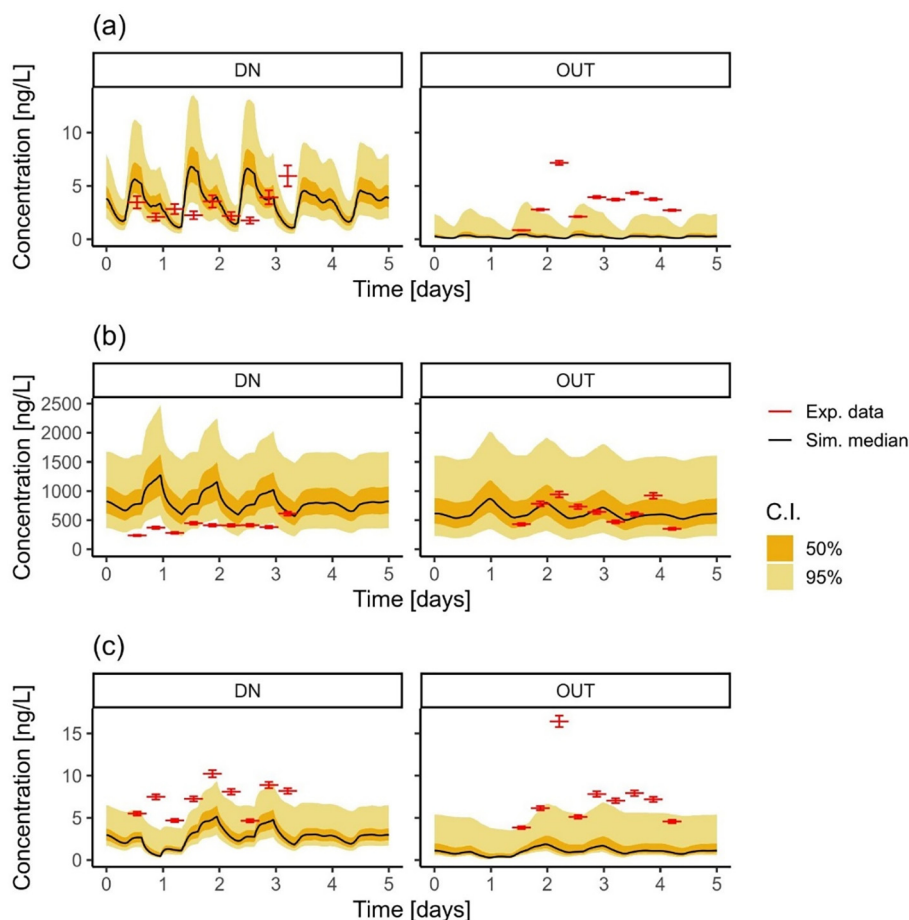


Fig. 4. Measurements and predictions of the literature-based models of E1 (a), DCF (b) and ERY (c) concentrations between the anoxic and aerated reactors (DN) and at the outlet of the secondary settler (OUT). E2 is not shown as present at concentrations below LOQ at both DN and OUT.

ecotoxicity effects. Noticeably, while both uncertainty analyses show comparable predicted DCF concentrations at sampling point DN and OUT, the measured values present an increase between the anoxic and the anaerobic which could be due to the de-conjugation of less/degradable metabolites and/or the release of sequestered DCF from feces, highlighting the need for the proper description of these processes which, however, lies beyond the scope of this study (Delli Compagni et al., 2020b; Kumar et al., 2022).

As highlighted earlier, parameters estimated from a given WWTP might not be appropriate to model the CECs removal in others. However, even though the DoE-based simulations were built on experimental data originating from a single WWTP, results still matched measured concentrations with satisfactory accuracy, as hypothesized based on the results of Baalbaki et al. (2017b).

To better appreciate the difference between the results of the DoE-based and literature-based simulations, Table 3 shows the mean absolute difference between measured and simulated composite samples concentrations for both models and all samples collected. While the DoE-based models did not result in a drastic improvement of the average absolute difference

with respect to the literature-based models, they generically led to lower prediction uncertainty. Noteworthy, the DoE-based uncertainty analysis reduced both the mean normalized absolute difference and its standard deviation between sampling point DN and OUT for all CECs, while this was not the case for the literature-based one. This result highlights how the inclusion of operational parameters in CEC fate modelling derived from the analysis of a single WWTP can provide comparable, if not superior, generalization compared to the use of literature values collected from several WWTPs without accounting for the operational parameters. The greater prediction uncertainty determined by the literature-based models reflects the variability present within the literature where values for single CECs can span over 2 orders of magnitude (Pomiès et al., 2013) due to the variety of experimental conditions. Such heterogeneity results in the fact that, when searching for literature values to use in a WWTP model, many of the values found are likely not applicable to the specific WWTP modelled due to the presence of different operational parameters. Carrying out an uncertainty analysis using all the parameter values found in literature, on one hand, can aid to include measurements within the uncertainty bounds, but,

Table 3

Mean and standard deviation of the absolute difference [ng/L] between the measured composite samples concentration and the simulated ones. Values normalized with the measured concentrations are reported in brackets. E2 is not included as all measurements were below LOQ.

Model	E1		DCF		ERY	
	DoE	Literature	DoE	Literature	DoE	Literature
DN	4.25 ± 0.41 (1.37 ± 0.13)	2.15 ± 3.72 (0.69 ± 1.2)	421.68 ± 44.12 (1.06 ± 0.11)	514.89 ± 126.47 (1.30 ± 0.32)	6.01 ± 1.31 (0.83 ± 0.18)	4.16 ± 0.41 (0.58 ± 0.06)
OUT	2.78 ± 0.38 (0.8 ± 0.11)	3.03 ± 0.30 (0.87 ± 0.09)	179.54 ± 50.11 (0.27 ± 0.08)	163.70 ± 125.43 (0.25 ± 0.19)	3.19 ± 0.42 (0.43 ± 0.06)	5.62 ± 0.45 (0.78 ± 0.06)

on the other, it leads to an overestimation of the uncertainty due to the variability of experimental conditions in which those values were obtained, reflecting the trade-off between precision and accuracy. In fact, the use of model performance metrics, which include the uncertainty in both measurements and simulations, should be favoured. For instance, the estimation of RMSE through the Interval-Deviation Approach (Chen et al., 2014) (Table S10) allowed to draw similar conclusions to the ones obtained from Table 3.

Considering these results, we argue that modellers should not target only the inclusion of the measurement values within the uncertainty bounds, as large uncertainty bounds limit the usefulness of the results to inform WWTP managers and regulators on CEC fate and to discriminate between the prediction of the outcome of possible interventions. Conversely, in case overestimated uncertainty bounds are present, modellers should focus on identifying their sources to identify a possible knowledge gap which would then be addressed. Finally, it needs to be noted that the absolute differences present in Table 3, might be excessive for specific practical applications (e.g., assessment of legislative compliance), highlighting, on one side, the difficulties connected with CEC WWTP modelling and, on the other, benefits of the combined use of both models and direct measurements.

We speculate that the limited improvement resulting from the use of more complex models is related to the fact that some of the operational parameters in the modelled full-scale WWTP were outside the ranges used to develop the DoE-based models (i.e., pH: 7.8–7.9 and TSS: 6.2–6.4) and were also largely stable within the monitored period, leading to approximately constant estimated biodegradation and sorption rates (Figs. S10 and S11). The higher complexity and development costs of the proposed methodology, however, could allow the simulation of dynamic events (e.g., due to rainfall) or long-term periods (e.g., seasonal changes) where constant sorption and biodegradation parameters are inadequate. In fact, several monitoring campaigns have found that either the presence of rainfall or the change of the operating conditions linked

with different seasons result in the variation of the WWTP removal rates (Castaño-Trias et al., 2020; Fernández et al., 2014; Sui et al., 2011, 2015; Vieno et al., 2007).

3.4. Exploring the effect of operating conditions on CECs removal

The developed DoE-based models allow to estimate the effect of operational parameters on the CECs removal. As it is shown in Figs. 5a and S12, removal percentage can vary up to 50 % depending on WWTP conditions, in accordance with the great variability found in literature (Tran et al., 2018). It can also be noted how, for few CECs (i.e., MTC), several optimal configurations exist, possibly due to the presence of interactions among different operational parameters. In addition, it is possible to observe how sorption can result higher wasted sludge CEC concentrations than in the influent wastewater (Figs. 5b and S13). While such process helps to remove CECs from the effluent, an excessive CECs accumulation in sludge will pose problems during its possible reuse in agriculture (Kinney et al., 2006), requiring the adoption of appropriate pre-treatments (Malmberg and Magnér, 2015). Whenever possible, WWTP managers should thus favour the removal of CECs from the water phase through biodegradation and not through sorption. Sludge stabilization through anaerobic and aerobic processes (beyond the scope of this study) may positively contribute to increasing CEC removal through biodegradation.

As different CECs have contrasting optima for their removal, a unique optimal configuration cannot be established. In any case, depending on the site-specific influent CEC concentrations, operational parameters should target the compliance with the imposed effluent limits and, furthermore, the minimization of the overall ecotoxicity of the effluent and of the wasted sludge. This goal should be based on an environmental risk assessment (ERA) including both acute and chronic effects, since predicted no-effect concentrations differ between the two modes of action (Vestel et al., 2016), and the presence of CECs transformation products (Escher and Fenner, 2011).

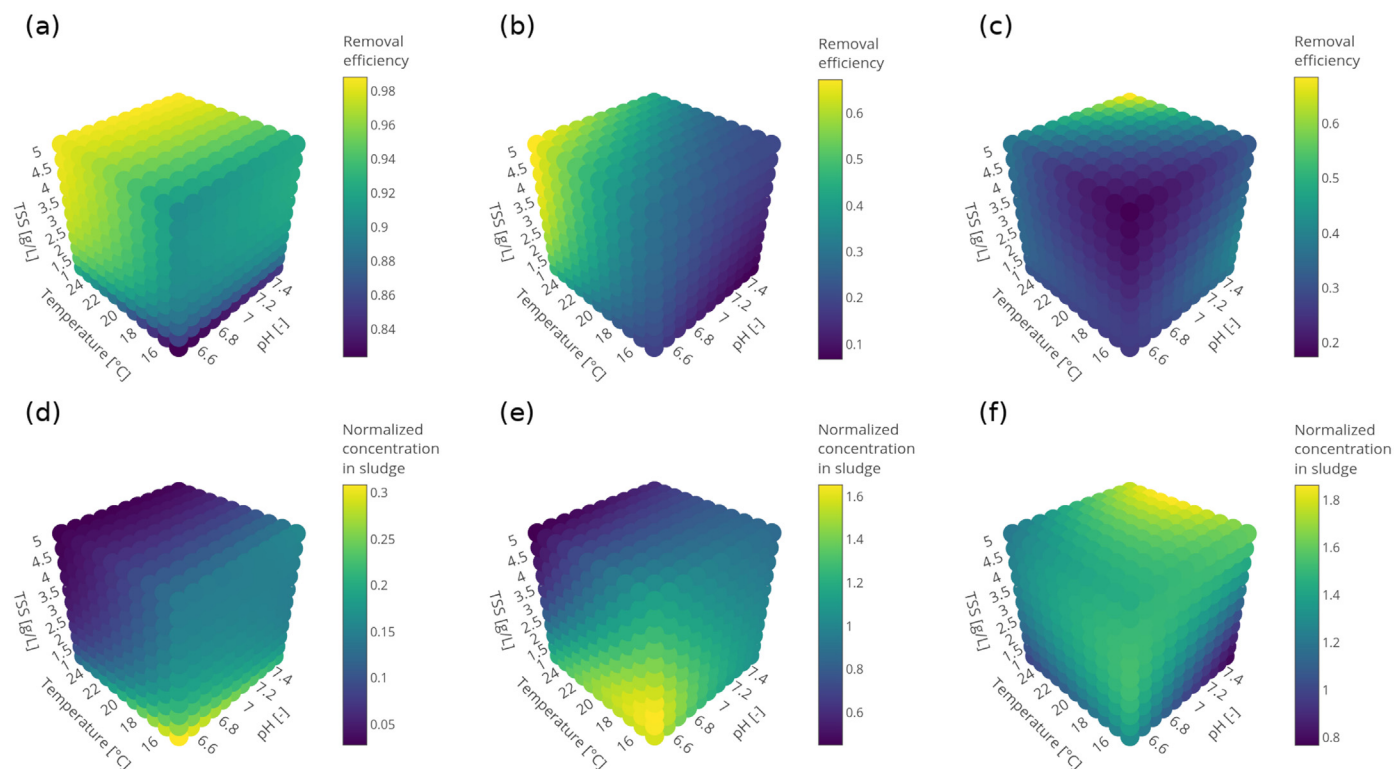


Fig. 5. Effect of TSS, temperature and pH on the removal percentages (a, b, c) and concentration in wasted sludge normalized to the influent concentration (d, e, f) for E1 (a, d), DCF (b, e) and ERY (c, f). The SRT connected to the tested TSS concentrations range from 5.5 to 40.5 d, while HRT ranged in the anoxic tank between 1.78 and 1.83 h and between 5.40 and 5.56 h in the aerobic one. Maximum standard deviations of removal percentages and normalized sludge concentrations equal to 0.01, 0.15, 0.08 and 0.06, 0.24 and 0.44 for E1, DCF and ERY, respectively.

Our simulations show that, in accordance with the general guidelines provided Krzeminski et al. (2019), an increased value of TSS is beneficial for the removal of all simulated CECs with the exception of CLT. Notably, except for CLT and ERY, the improved removal due to increased TSS concentration did not result in a concentration increment in the wasted sludge with most operating parameters combinations (Fig. S13), effectively enhancing CECs removal through biodegradation and not sorption. Furthermore, as the redox conditions were found to affect sorption and biodegradation of most CECs both directly and through interaction with other parameters (Fig. 1), adjusting the ratio between anoxic and aerobic conditions could provide a further option to improve CECs removal, even though of only minor importance with the tested CECs (Fig. S14). While this latter strategy can already be implemented in few WWTPs, a proper evaluation between the costs and the benefits should be undertaken in case a structural upgrade would be needed, in order to take into account other possible impacts of this choice. In particular, the achievement of optimal configurations and operational parameters for CECs removal should not impair the removal of conventional pollutants (Lopez-Vazquez et al., 2009) or overall functionality (e.g., bulking), thus leading to unsustainable WWTP management costs.

4. Conclusions

The effect of several operational parameters (i.e., pH, total suspended solids, temperature, and redox conditions) on sorption and biodegradation in laboratory-scale experiments was successfully included in statistical models relying on the DoE methodology, highlighting how both sorption and biodegradation are affected by several parameters and their interactions. The comparison between the models results and data retrieved from literature highlighted how the inclusion of the mentioned operational parameters allows a successful generalization regarding CECs sorption characteristics, but not for biodegradation as highly influenced by WWTP-specific conditions other than the operational parameters tested. In any case, the proposed DoE-based modelling approach allowed to successfully simulate CECs fate in a full-scale WWTP different from the one sampled to develop the DoE-based models. When compared to a traditional literature-based uncertainty analysis, the use of the developed statistical models provided comparable accuracy in predicting CECs concentration and a three-fold reduction of the uncertainty bounds, stressing the importance of the trade-off between precision and accuracy for the effective use of WWTP models by WWTP managers and regulators and the benefit to integrate modelling results with direct measurements. Finally, the developed DoE-based models were used to point out that, while generically higher temperatures and TSS concentrations favour CECs removal, globally optimum operational parameters do not exist. In fact, such conditions should be evaluated locally on the base of the CECs concentrations and on the effluent ecotoxicological risk.

The application of the developed DoE-based models and methodology opens interesting perspectives for researchers and/or WWTP managers to include CEC removal as an optimization goal alongside the fulfilment of conventional pollutants emission limits and the minimization of operational costs, and to perform simulations characterized by drastic changes in the operational parameters within WWTPs. In addition, by comparing the results of DoE-based models obtained from different WWTPs, such methodology could be used to provide fruitful insights regarding CEC fate in WWTPs discerning between site-specific and ubiquitous effects.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2022.159200>.

CRedit authorship contribution statement

Marco Gabrielli: Methodology, Software, Writing – original draft, Visualization. **Riccardo Delli Compagni:** Conceptualization, Methodology, Writing – review & editing. **Lucia Gusmaroli:** Investigation, Writing – review & editing. **Francesca Malpei:** Writing – review & editing. **Fabio Polesel:** Writing – review & editing. **Gianluigi Buttiglieri:** Investigation,

Resources, Writing – review & editing, Funding acquisition. **Manuela Antonelli:** Writing – review & editing, Funding acquisition. **Andrea Turolla:** Conceptualization, Investigation, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study has received funding from the Spanish State Research Agency (ReUseMP3; PID2020-115456RB-I00). ICRA researchers thank the funding of the CERCA program.

References

- Achermann, S., et al., 2020. Relating metatranscriptomic profiles to the micropollutant biotransformation potential of complex microbial communities. *Environ. Sci. Technol.* 54, 235–244. <https://doi.org/10.1021/acs.est.9b05421>.
- Alvarino, T., et al., 2014. Understanding the removal mechanisms of PPCPs and the influence of main technological parameters in anaerobic UASB and aerobic CAS reactors. *J. Hazard. Mater.* 278, 506–513. <https://doi.org/10.1016/j.jhazmat.2014.06.031>.
- Australia, 2008. Australian Guidelines for Water Recycling: Managing Health and Environmental Risks (Phase 2): Augmentation of Drinking Water Supplies. Natural Resource Management Ministerial Council: Environment Protection and Heritage Council, Canberra.
- Baalbaki, Z., et al., 2017a. Dynamic modelling of solids in a full-scale activated sludge plant preceded by CEPT as a preliminary step for micropollutant removal modelling. *Bioprocess Eng.* 40, 499–510. <https://doi.org/10.1007/s00449-016-1715-5>.
- Baalbaki, et al., 2017. Predicting the fate of micropollutants during wastewater treatment: calibration and sensitivity analysis. *Sci. Total Environ.* 601–602, 874–885. <https://doi.org/10.1016/j.scitotenv.2017.05.072>.
- Banihashemi, B., Droste, R.L., 2014. Sorption–desorption and biosorption of bisphenol A, triclosan, and 17 α -ethinylestradiol to sewage sludge. *Sci. Total Environ.* 487, 813–821. <https://doi.org/10.1016/j.scitotenv.2013.12.116>.
- Barret, M., et al., 2010. Micropollutant and sludge characterization for modeling sorption equilibria. *Environ. Sci. Technol.* 44, 1100–1106. <https://doi.org/10.1021/es902575d>.
- Berthod, L., et al., 2016. Effect of sewage sludge type on the partitioning behaviour of pharmaceuticals: a meta-analysis. *Environ. Sci.: Water Res. Technol.* 2, 154–163. <https://doi.org/10.1039/C5EW00171D>.
- Blair, B.D., et al., 2013. Evaluation of a model for the removal of pharmaceuticals, personal care products, and hormones from wastewater. *Sci. Total Environ.* 444, 515–521. <https://doi.org/10.1016/j.scitotenv.2012.11.103>.
- California, 2019. California Statutes Related to Recycled Water & the State Board's Division of Drinking Water.
- Canada, 2021. Canadian Environmental Protection Act.
- Cantoni, B., et al., 2020. A statistical assessment of micropollutants occurrence, time trend, fate and human health risk using left-censored water quality data. *Chemosphere* 257, 127095. <https://doi.org/10.1016/j.chemosphere.2020.127095>.
- Castañón-Trias, M., et al., 2020. Fate and removal of pharmaceuticals in CAS for water and sewage sludge reuse. *The Handbook of Environmental Chemistry, First edition Springer, Switzerland*.
- Chen, L., et al., 2014. An interval-deviation approach for hydrology and water quality model evaluation within an uncertainty framework. *J. Hydrol.* 509, 207–214. <https://doi.org/10.1016/j.jhydrol.2013.11.043>.
- Chiang, Y., et al., 2020. Microbial degradation of steroid sex hormones: implications for environmental and ecological studies. *Microb. Biotechnol.* 13, 926–949. <https://doi.org/10.1111/1751-7915.13504>.
- Clara, M., et al., 2004. Adsorption of bisphenol-A, 17 β -estradiol and 17 α -ethinylestradiol to sewage sludge. *Chemosphere* 56, 843–851. <https://doi.org/10.1016/j.chemosphere.2004.04.048>.
- Collado, N., et al., 2012. Removal of ibuprofen and its transformation products: experimental and simulation studies. *Sci. Total Environ.* 433, 296–301.
- Daughton, C.G., Ternes, T.A., 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? *Environ. Health Perspect.* 107, 32.
- de Boer, S., et al., 2022. Benchmarking tertiary water treatments for the removal of micropollutants and pathogens based on operational and sustainability criteria. *J. Water Process Eng.* 46, 102587. <https://doi.org/10.1016/j.jwpe.2022.102587>.
- de Wilt, A., et al., 2018. Sorption and biodegradation of six pharmaceutically active compounds under four different redox conditions. *Chemosphere* 193, 811–819. <https://doi.org/10.1016/j.chemosphere.2017.11.084>.

- Delli Compagni, R., et al., 2020a. Risk assessment of contaminants of emerging concern in the context of wastewater reuse for irrigation: an integrated modelling approach. *Chemosphere* 242, 125185. <https://doi.org/10.1016/j.chemosphere.2019.125185>.
- Delli Compagni, R., et al., 2020b. Modelling the fate of micropollutants in integrated urban wastewater systems: extending the applicability to pharmaceuticals. *Water Res.* 184, 116097. <https://doi.org/10.1016/j.watres.2020.116097>.
- Dominguez Henao, L., et al., 2018. Influence of inorganic and organic compounds on the decay of peracetic acid in wastewater disinfection. *Chem. Eng. J.* 337, 133–142. <https://doi.org/10.1016/j.cej.2017.12.074>.
- Escher, B.I., Fenner, K., 2011. Recent advances in environmental risk assessment of transformation products. *Environ. Sci. Technol.* 45, 3835–3847. <https://doi.org/10.1021/es1030799>.
- European Commission, 2012. **Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL Amending Directives 2000/60/EC and 2008/105/EC as Regards Priority Substances in the Field of Water Policy.**
- European Commission, 2020. **REGULATION (EU) 2020/741 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 May 2020 on Minimum Requirements for Water Reuse.**
- Fernández, M.F., et al., 2014. Seasonal occurrence and removal of pharmaceutical products in municipal wastewater systems. *J. Environ. Chem. Eng.* 2, 495–502. <https://doi.org/10.1016/j.jece.2014.01.023>.
- Gulde, R., et al., 2014. pH-dependent biotransformation of ionizable organic micropollutants in activated sludge. *Environ. Sci. Technol.* 48, 13760–13768. <https://doi.org/10.1021/es5037139>.
- Guo, L., Vanrolleghem, P.A., 2014. Calibration and validation of an activated sludge model for greenhouse gases no. 1 (ASM-G1): prediction of temperature-dependent N_2O emission dynamics. *Bioprocess. Biosyst. Eng.* 37 (2), 151–163. <https://doi.org/10.1007/s00449-013-0978-3> 2014 Feb.
- Gusmaroli, L., et al., 2018. Development of an online SPE-UHPLC-MS/MS method for the multiresidue analysis of the 17 compounds from the EU “Watch list”. *Anal. Bioanal. Chem.* 410, 4165–4176. <https://doi.org/10.1007/s00216-018-1069-8>.
- Gusmaroli, L., et al., 2020. How do WWTPs operational parameters affect the removal rates of EU Watch list compounds? *Sci. Total Environ.* 714, 136773. <https://doi.org/10.1016/j.scitotenv.2020.136773>.
- Hatoum, P., et al., 2019. Elimination of micropollutants in activated sludge reactors with a special focus on the effect of biomass concentration. *Water* 11, 2217. <https://doi.org/10.3390/w11112217>.
- Hauduc, H., et al., 2009. Activated sludge modelling in practice: an international survey. *Water Sci. Technol.* 60, 1943–1951. <https://doi.org/10.2166/wst.2009.223>.
- Helsel, D.R., 2011. *Statistics for Censored Environmental Data Using Minitab(R) AND R*. Second edition. John Wiley & Sons, Inc., Hoboken, NJ, USA <https://doi.org/10.1002/9781118162729.fmatter>.
- Ho, L., et al., 2019. A practical protocol for the experimental design of comparative studies on water treatment. *Water* 11, 162. <https://doi.org/10.3390/w11010162>.
- Hörsing, M., et al., 2011. Determination of sorption of seventy-five pharmaceuticals in sewage sludge. *Water Res.* 45, 4470–4482. <https://doi.org/10.1016/j.watres.2011.05.033>.
- Johnson, D.R., et al., 2015. Association of biodiversity with the rates of micropollutant biotransformations among full-scale wastewater treatment plant communities. *Appl. Environ. Microbiol.* 81, 666–675. <https://doi.org/10.1128/AEM.03286-14>.
- Jones, O.A.H., et al., 2007. Questioning the excessive use of advanced treatment to remove organic micropollutants from wastewater. *Environ. Sci. Technol.* 41, 5085–5089. <https://doi.org/10.1021/es0628248>.
- Joss, A., et al., 2004. Removal of estrogens in municipal wastewater treatment under aerobic and anaerobic conditions: consequences for plant optimization. *Environ. Sci. Technol.* 38, 3047–3055. <https://doi.org/10.1021/es0351488>.
- Kennes-Veiga, D.M., et al., 2022. Enzymatic cometabolic biotransformation of organic micropollutants in wastewater treatment plants: a review. *Bioresour. Technol.* 344, B, 126291.
- Kinney, C.A., et al., 2006. Survey of organic wastewater contaminants in biosolids destined for land application. *Environ. Sci. Technol.* 40, 7207–7215. <https://doi.org/10.1021/es0603406>.
- Krzeminski, P., et al., 2019. Performance of secondary wastewater treatment methods for the removal of contaminants of emerging concern implicated in crop uptake and antibiotic resistance spread: a review. *Sci. Total Environ.* 648, 1052–1081. <https://doi.org/10.1016/j.scitotenv.2018.08.130>.
- Kumar, M., Ngasepam, J., Dhangar, K., Mahlknecht, J., Manna, S., 2022. Critical review on negative emerging contaminant removal efficiency of wastewater treatment systems: concept, consistency and consequences. *Bioresour. Technol.* 352, 127054. <https://doi.org/10.1016/j.biortech.2022.127054>.
- Li, F., Yuasa, A., Obara, A., Mathews, A.P., 2005. Aerobic batch degradation of 17- β -estradiol (E2) by activated sludge: effects of spiking E2 concentrations, MLVSS and temperatures. *Water Res.* 39, 2065–2075. <https://doi.org/10.1016/j.watres.2005.02.009>.
- Lopez-Vazquez, C.M., et al., 2009. Modeling the PAO–GAO competition: effects of carbon source, pH and temperature. *Water Res.* 43, 450–462. <https://doi.org/10.1016/j.watres.2008.10.032>.
- Malmberg, J., Magnér, J., 2015. Pharmaceutical residues in sewage sludge: effect of sanitization and anaerobic digestion. *J. Environ. Manag.* 153, 1–10. <https://doi.org/10.1016/j.jenvman.2015.01.041>.
- Meynet, P., et al., 2020. Understanding the dependence of micropollutant biotransformation rates on short-term temperature shifts. *Environ. Sci. Technol.* 54, 12214–12225. <https://doi.org/10.1021/acs.est.0c04017>.
- Montgomery, D.C., 2017. *Design and Analysis of Experiments*. Ninth edition. John Wiley & Sons, Hoboken, USA.
- Newville, Matthew, et al., 2014. *LMFIT: Non-Linear Least-Square Minimization and Curve-Fitting for Python*.
- Nolte, T.M., Ragas, A.M.J., 2017. A review of quantitative structure-property relationships for the fate of ionizable organic chemicals in water matrices and identification of knowledge gaps. *Environ. Sci. Processes Impacts* 19 (3), 221–246. <https://doi.org/10.1039/C7EM00034K>.
- Nolte, T.M., et al., 2020. Disentanglement of the chemical, physical, and biological processes aids the development of quantitative structure-biodegradation relationships for aerobic wastewater treatment. *Sci. Total Environ.* 708, 133863. <https://doi.org/10.1016/j.scitotenv.2019.133863>.
- Petrie, B., et al., 2014. Diagnostic investigation of steroid estrogen removal by activated sludge at varying solids retention time. *Chemosphere* 113, 101–108. <https://doi.org/10.1016/j.chemosphere.2014.04.051>.
- Plósz, B.Gy, et al., 2010a. Diurnal variations in the occurrence and the fate of hormones and antibiotics in activated sludge wastewater treatment in Oslo, Norway. *Sci. Total Environ.* 408, 1915–1924. <https://doi.org/10.1016/j.scitotenv.2010.01.042>.
- Plósz, B.Gy, et al., 2010b. Impacts of competitive inhibition, parent compound formation and partitioning behavior on the removal of antibiotics in municipal wastewater treatment. *Environ. Sci. Technol.* 44, 734–742. <https://doi.org/10.1021/es902264w>.
- Plósz, B.Gy, et al., 2012. An activated sludge modeling framework for xenobiotic trace chemicals (ASM-X): assessment of diclofenac and carbamazepine. *Biotechnol. Bioeng.* 109, 2757–2769. <https://doi.org/10.1002/bit.24553>.
- Polesel, F., et al., 2015. Factors influencing sorption of ciprofloxacin onto activated sludge: experimental assessment and modelling implications. *Chemosphere* 119, 105–111. <https://doi.org/10.1016/j.chemosphere.2014.05.048>.
- Pomiś, M., et al., 2013. Modelling of micropollutant removal in biological wastewater treatments: a review. *Sci. Total Environ.* 443, 733–748. <https://doi.org/10.1016/j.scitotenv.2012.11.037>.
- Ramin, P., et al., 2016. Transformation and sorption of illicit drug biomarkers in sewer systems: understanding the role of suspended solids in raw wastewater. *Environ. Sci. Technol.* 50, 13397–13408. <https://doi.org/10.1021/acs.est.6b03049>.
- Ramin, P., et al., 2018. The impact of temperature on the transformation of illicit drug biomarkers in wastewater. *Sci. Total Environ.* 644, 1612–1616.
- Rieger, L., et al., 2013. *Guidelines for Using Activated Sludge Models (Scientific and Technical Report No. 22)*. IWA Publishing, London, UK.
- Rizzo, L., et al., 2019. Consolidated vs new advanced treatment methods for the removal of contaminants of emerging concern from urban wastewater. *Sci. Total Environ.* 655, 986–1008. <https://doi.org/10.1016/j.scitotenv.2018.11.265>.
- Sathiyamoorthy, S., Ramsburg, C.A., 2013. Assessment of quantitative structural property relationships for prediction of pharmaceutical sorption during biological wastewater treatment. *Chemosphere* 92, 639–646. <https://doi.org/10.1016/j.chemosphere.2013.01.061>.
- Struijs, J., et al., 2016. Adapting SimpleTreat for simulating behaviour of chemical substances during industrial sewage treatment. *Chemosphere* 159, 619–627. <https://doi.org/10.1016/j.chemosphere.2016.06.063>.
- Sui, Q., et al., 2011. Seasonal variation in the occurrence and removal of pharmaceuticals and personal care products in different biological wastewater treatment processes. *Environ. Sci. Technol.* 45, 3341–3348. <https://doi.org/10.1021/es200248d>.
- Sui, Q., et al., 2015. Pharmaceuticals and consumer products in four wastewater treatment plants in urban and suburb areas of Shanghai. *Environ. Sci. Pollut. Res.* 22, 6086–6094. <https://doi.org/10.1007/s11356-014-3793-8>.
- Sürlüci, G., Çetin, F.D., 1990. Effects of temperature, pH and D. O. concentration on settleability of activated sludge. *Environ. Technol.* 11, 205–212. <https://doi.org/10.1080/09593339009384858>.
- Swiss Federal Council, 2020. **Waters Protection Ordinance.**
- Tadkaew, N., et al., 2010. Effect of mixed liquor pH on the removal of trace organic contaminants in a membrane bioreactor. *Bioresour. Technol.* 101, 1494–1500. <https://doi.org/10.1016/j.biortech.2009.09.082>.
- Ternes, T., Joss, A. (Eds.), 2006. *Human Pharmaceuticals, Hormones and Fragrances - The Challenge of Micropollutants in Urban Water Management*. IWA Publishing.
- Therneau, T., 2020. *A Package for Survival Analysis in R*.
- Tran, N.H., et al., 2013. Insight into metabolic and cometabolic activities of autotrophic and heterotrophic microorganisms in the biodegradation of emerging trace organic contaminants. *Bioresour. Technol.* 146, 721–731. <https://doi.org/10.1016/j.biortech.2013.07.083>.
- Tran, N.H., et al., 2018. Occurrence and fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions—a review. *Water Res.* 133, 182–207. <https://doi.org/10.1016/j.watres.2017.12.029>.
- Urase, T., Kikuta, T., 2005. Separate estimation of adsorption and degradation of pharmaceutical substances and estrogens in the activated sludge process. *Water Res.* 39, 1289–1300. <https://doi.org/10.1016/j.watres.2005.01.015>.
- Venables, W.N., Ripley, B.D., 2002. *Modern Applied Statistics With S*. Fourth edition. Springer, New York, USA.
- Verlicchi, P., et al., 2012. Occurrence of pharmaceutical compounds in urban wastewater: removal, mass load and environmental risk after a secondary treatment—a review. *Sci. Total Environ.* 429, 123–155. <https://doi.org/10.1016/j.scitotenv.2012.04.028>.
- Vestel, J., et al., 2016. Use of acute and chronic ecotoxicity data in environmental risk assessment of pharmaceuticals. *Environ. Toxicol. Chem.* 35, 1201–1212. <https://doi.org/10.1002/etc.3260>.
- Vezzaro, L., et al., 2014. A model library for dynamic transport and fate of micropollutants in integrated urban wastewater and stormwater systems. *Environ. Model Softw.* 53, 98–111. <https://doi.org/10.1016/j.envsoft.2013.11.010>.
- Vieno, N., et al., 2007. Elimination of pharmaceuticals in sewage treatment plants in Finland. *Water Res.* 41, 1001–1012. <https://doi.org/10.1016/j.watres.2006.12.017>.
- Wang, X., et al., 2012. Pyrosequencing analysis of bacterial diversity in 14 wastewater treatment systems in China. *Appl. Environ. Microbiol.* 78, 7042–7047. <https://doi.org/10.1128/AEM.01617-12>.

- Weissman, S.A., Anderson, N.G., 2015. Design of experiments (DoE) and process optimization. A review of recent publications. *Org. Process. Res. Dev.* 19, 1605–1633. <https://doi.org/10.1021/op500169m>.
- Xu, K., et al., 2008. 17 α -Ethinylestradiol sorption to activated sludge biomass: thermodynamic properties and reaction mechanisms. *Water Res.* 42, 3146–3152. <https://doi.org/10.1016/j.watres.2008.03.005>.
- Xu, Y., et al., 2021. Sorption of pharmaceuticals and personal care products on soil and soil components: influencing factors and mechanisms. *Sci. Total Environ.* 753, 141891. <https://doi.org/10.1016/j.scitotenv.2020.141891>.
- Xue, W., et al., 2010. Elimination and fate of selected micro-organic pollutants in a full-scale anaerobic/anoxic/aerobic process combined with membrane bioreactor for municipal wastewater reclamation. *Water Res.* 44, 5999–6010. <https://doi.org/10.1016/j.watres.2010.07.052>.
- Zhang, T., et al., 2005. Effect of pH change on the performance and microbial community of enhanced biological phosphate removal process. *Biotechnol. Bioeng.* 92, 173–182. <https://doi.org/10.1002/bit.20589>.
- Zhang, M., et al., 2020. Sorption of pharmaceuticals and personal care products (PPCPs) from water and wastewater by carbonaceous materials: a review. *Crit. Rev. Environ. Sci. Technol.* 1–40. <https://doi.org/10.1080/10643389.2020.1835436>.
- Zhou, X., et al., 2013. Partitioning of fluoroquinolones on wastewater sludge. *Clean Soil Air Water* 41, 820–827. <https://doi.org/10.1002/clen.201100731>.